copy of the amended portion of the specification.

IN THE CLAIMS

Please amend claims 1 and 3 as indicated in Appendices C and D submitted herewith. Appendix C is a marked-up copy of the amended claims and Appendix D is a clean copy of the amended claims.

REMARKS

Claims 1 and 3 and 16-24 are currently pending in the present application. Claims 2 and 8-15 have been withdrawn from consideration and claims 4-7 have been cancelled. Claim 1 is an independent claim. Claim 3 has also been amended to be an independent claim.

The specification is objected to because of a missing space. Claim 7 is objected to under 37 CFR 1.75 as being an improper multiple dependent claim. The claims are objected to because of unspecified abbreviations which allegedly appear without prior definition. Claims 1 and 3 are rejected under 35 USC §101 as being directed to non-statutory subject matter. Claims 1 and 4-6 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. Claims 1,3-5 are rejected under 35 USC §102(e) as being anticipated over Meinersmann et al and Schultz et al. Claims 1 and 3 are rejected under 35 USC §102(b) as being anticipated over Alm et al. Claims 1 and 3 are also rejected under 35 USC §102(b) as being anticipated over Rasmussen.

By this Amendment, the specification and claims 1 and 3 are amended and claims 4-7 are cancelled, thus overcoming the objections to the specification and claims as well as the 35 U.S.C. §112, second paragraph and 35 USC §102(e) and 35 USC §102(b) rejections. No new matter has been added. Applicants contend that the amendments and response place the claims in better condition for allowance.

Accordingly, an allowance of all pending claims is respectfully requested.

1. OBJECTION TO SPECIFICATION

The specification is objected to because a blank space is present at page 19, line 21. By this Amendment, the specification is amended to remove the blank space, thus obviating the objection. Applicants' respectfully request the objection be withdrawn.

2. OBJECTION TO CLAIMS

Claim 7 is objected to because it is in improper multiple dependent form because its dependency is not in the alternative. By this Amendment, Claim 7 is cancelled, thus obviating the objection. Applicants' respectfully request the objection be withdrawn. Abbreviations (ie. pMal-c2, pMal-p2 and pET) are also objected to in claim 6 as being trade names. Applicants have cancelled claim 6; however, the specification has been amended to provide generic language for these vectors and the names have

been capitalized to reflect the status of these vectors as tradenames.

Applicants respectfully request the objection be withdrawn.

3. REJECTION OF CLAIMS 1 AND 3 UNDER 35 U.S.C. §101

Claims 1 and 3 are rejected under 35 U.S.C. §101 as being drawn to non-statutory subject matter as the claimed polynucleotide sequences are not isolated and purified. By this Amendment, Claims 1 and 3 are amended to add the limitations "isolated and purified", thus overcoming the rejection. Applicants respectfully request the rejection be withdrawn.

4. REJECTION OF CLAIMS 1 and 4-6 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1 and 4-6 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. As a basis for this rejection, the Office Action states:

> Claim 1 is directed to a polynucleotide sequence encoding a polypeptide that is a portion of flaA. A portion that encodes a flaA polypeptide would be at least 6 nucleotides in length, to encode a two amino acid containing polypeptide. Moreover, the rejection questions the utility of a two amino acid polypeptide. The rejection also questions where the location of the non-coding region of the polynucleotide is. Claim 4 is stated to be indefinite because it recites an expression vector wherein the polypeptide of claim 1 is inserted. The rejection also questions why both an expression system and vector are recited in the claim when they both have the same components. Claim 5 is stated to be indefinite because the Markush group language is not set forth for the species recited. Claim 6 is improper because it appears that the plasmid abbreviations are tradenames.

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RESPONSE

By this Amendment, Claims 1 is amended and claims 4-6 are cancelled, thus overcoming the rejection.

Amended claim 1 is directed to an "isolated and purified" polynucleotide sequence encoding an immunogenic polypeptide that is a portion of the flaA coding region of Campylobacter, said polynucleotide sequence comprising nucleotides 13-1015 of the DNA sequence of SEQ ID NO. 1, which contains the necessary regulatory sequences.

The rejection also states that claim 1 uses open and closed ended language, thus clarification was sought as to whether an additional portion of the flaA gene was being claimed beyond the scope of SEQ ID NO. 1.

Applicants amended claim 1 is limited to the specific residues of SEQ ID NO. 1, nucleotides 13-1015, which is a highly conserved region which also forms a part of the flaA gene. However, Applicants do not seek to claim a region of the flaA gene outside the scope of these claimed residues. Thus, Applicants contend amended claim 1 is not indefinite and that it more clearly and distinctly claims what Applicants are seeking to patent.

Claims 4-6 have been cancelled rendering those rejections moot.

Applicants' respectfully request the rejection of independent

claim 1 and dependent claims 4-6 be reconsidered and withdrawn.

5. REJECTION OF CLAIMS 1, and 3-5 UNDER 35 U.S.C. §102(e)

Claims 1, 3-5 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated and unpatentable over Meinersmann et al (U.S. Pat. 5,837,825). The rejection states:

> Meinersmann discloses an isolated polynucleotide sequence that encodes a polypeptide, wherein the polypeptide is encoded by the truncated portion of Campylobacter flaA gene. The disclosed portion is alleged to be truncated at both the 5' and 3'ends and is 1.1 kb polynucleotide of Campylobacter (col.9, lines 1-16) Meinersmann is also alleged to disclose an isolated polynucleotide that encodes for a portion of Campylobacter FlaA polypeptide that was inserted into a lambda bacteriophage vector (col.9, line 14), transferred to a plasmid (col. 9, line 19) and transformed in an E.coli expression system (col 9, line 47).

RESPONSE

By this Amendment, independent claims 1 and 3 are amended and claims 4 and 5 are cancelled. Amended claim 1 is directed to an isolated and purified polynucleotide sequence encoding a polypeptide that is a portion of the flaA coding region of Campylobacter, said polynucleotide sequence comprising nucleotides 13-1015 of the DNA sequence of SEQ ID NO. 1 which contains the necessary regulatory sequences. Newly amended independent claim 3 is drawn to a "isolated and purified" DNA sequence encoding an immunogenic polypeptide comprising amino acid residues 5-338 of SEQ ID No:2.

Applicants respectfully submit that the rejection does not

establish a prima facie case of anticipation under 35 U.S.C. §102(e) because Meinersmann fails to teach each and every element of independent claims 1 and 3.

Meinersmann discloses expression of part of flaA gene as a fusion to LTB for use as a chicken vaccine. The vaccine comprises a 1.1 kb region from the middle of the flaA gene which is not the same region of the flaA gene as claimed in independent claim 1. The 1.1 kb region aligns with our sequence at base pair 759/999 and extends beyond ours. Thus, Meinersmann fails to teach the specific nucleotides,13-1015, of SEQ ID NO. 1, as claimed in Claim 1 nor the specific DNA sequence encoding an immunogenic polypeptide comprising amino acid residues 5-338 of SEQ ID NO:2.

Thus, Meinersmann does not anticipate independent claims 1 nor 3. Thus, claims 1 and 3 must be patentable over Meinersmann.

Applicants respectfully request the rejection under 35 U.S.C. §102(e) be reconsidered and withdrawn.

6. REJECTION OF CLAIMS 1 and 3 UNDER 35 U.S.C. §102(e)

Claims 1 and 3 are rejected under 35 U.S.C. §102(e)as allegedly being anticipated by Schultz et al. (U.S. Pat. 6,270,974). The rejection states:

> Schultz discloses a polynucleotide sequence encoding a portion of the flaA gene of Campylobacter, wherein the polynucleotide sequence is a portion of the DNA sequence of SEQ ID No. 1. The rejection admits that the Schultz sequences shares 100% sequence identity over 30 nucleotides

of SEQ ID NO:1, and encodes amino acids 97-106 of SEQ ID NO:2.

RESPONSE

By this Amendment, claims 1 and 3 are amended. Amended claim 1 is directed to a polynucleotide sequence encoding a polypeptide that is a portion of the flaA coding region of Campylobacter, said polynucleotide sequence comprising nucleotides 13-1015 of the DNA sequence of SEQ ID NO. 1. Newly amended independent claim 3 is drawn to a "purified and isolated" DNA sequence encoding an immunogenic polypeptide comprising amino acid residues 5-338 of SEQ ID No:2.

The rejection of claims 1 and 3 fails to state a prima facie case of anticipation under 35 U.S.C. §102(e) because Schultz et al. fails to teach each and every element of claims 1 and 3.

Schultz discloses a rapid diagnostic method using probes for a number of infectious agents. Schultz also disclose a polynucleotide sequence that is a portion of the DNA sequence of SEQ ID NO: 1

Applicants contend that the Schultz patent fails to teach the specific polynucleotide sequence 13-1015 of SEQ ID NO.1 encoding the immunogenic polypeptide useful in reducing colonization of Campylobacter. Conversely, Schultz describes 4 probes/primers that are specific for detection of Campylobacter. The 4 probes/primers found within our coding sequence contain mismatches. Thus, primer #31 is identical to 56 out of the 60 bp

corresponding to bp 268-327 of our nucleotide sequence; primer #32 is identical to 28 out of the 30 bp between bp 289-318 of our sequence; primer 33 is identical to 56 out of the 61 bp between 268-327; and primer 34 is identical to 28 out of the 30 bp between 289-318. Thus, these 4 probes bind to overlapping regions that may have some similarity but are not identical to a subset of our sequence. They are designed to be used for diagnostic purposes rather than a vaccine or immunogenic composition. The fact that they can be used to identify campylobacter by PCR indicates that these subsets are conserved within strains, but does not suggest that they encode a protective polypeptide.

Accordingly, Schultz fails to teach the specific nucleotides of SEQ ID NO:1 in Claim 1 and the specific amino acids residues of SEQ ID NO: 2 in Claim 3. Thus, Schultz fails to teach each and every element of claim 1 and claim 3. Thus, claims 1 and 3 must be patentable over Schultz et al.

7. REJECTION OF CLAIMS 1 and 3 UNDER 35 U.S.C. §102(b)

Claims 1 and 3 are rejected under 35 U.S.C. §102(b)as allegedly being anticipated by Alm et al.(May 1993). The rejection states that Alm discloses a polynucleotide sequence encoding a portion of the flaA gene of Campylobacter, wherein the polynucleotide sequence is a portion of the DNA coding sequence for flaA obtained from C.coli VC167T-2. The rejection reasons that Alm's polynucleotide would comprise and share 100% sequence

identity with a portion of SEQ ID NO:1 and encode a portion of the amino acids of SEQ ID NO:2 because of endonuclease digestion of the flaA coding sequence.

Claims 1 and 3 are also rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Alm et al.(March 1993). Alm is alleged to disclose a polynucleotide sequence encoding a portion of the DNA coding sequence for flaA, wherein the nucleotide was an oligonucleotide portion of SEQ ID NO:1, specifically nucleotides starting at position 50 of SEQ ID NO:1 and ending at position 68 of SEQ ID NO:1. The rejection reasons that the Alm polynucleotide share 100% sequence identity with a portion of SEQ ID NO:1 and encodes a portion of the amino acids of SEQ ID NO:2.

RESPONSE

By this Amendment, Claims 1 and 3 are amended, thus overcoming the rejection of Alm et al (May 1993) and Alm et al (March 1993). Amended claim 1 is directed to an isolated and purified polynucleotide sequence encoding an immunogenic polypeptide that is a portion of the flaA gene of Campylobacter, said polynucleotide sequence consisting of nucleotides 13-1015 of the DNA sequence of SEQ ID NO. 1. Newly amended independent claim 3 is drawn to a "purified and isolated" DNA sequence encoding an immunogenic polypeptide comprising amino acid residues 5-338 of SEQ ID No:2.

Alm et al. discloses conserved and hypervariable domains of

flaA among strains of Campylobacter. Alm fails to teach the specific nucleotide sequence of SEQ ID NO: 1 of Claim 1 and the DNA sequence encoding the specific amino acid residues (5-338)of SEQ ID NO: 2 of Claim 3. Thus, Alm et al. fails to teach each and every element of Claims 1 and 3. There is no inherent feature of the teachings of Alm nor knowledge of those of skill in the art that could sufficiently supplement Alm's teachings to anticipate the specific sequences of the claimed invention.

Accordingly, Applicants respectfully request the rejections under 35 U.S.C. §102(b) be reconsidered and withdrawn.

Although the rejection does not state a rejection for obviousness under 35 U.S.C. §103, Applicants note that the rejection states a need to show Applicants' claimed compounds and compounds of the prior art do not show the same characteristics.

Applicants contend that Alm did not express truncated flagellins and certainly did not express the specific polynucleotide sequences taught in the instant specification.

Lastly, Alm fails to teach or suggest Applicants claimed utility of the claimed compounds providing protection against Campylobacter induced diarrhea.

8. REJECTION OF CLAIMS 1 and 3 UNDER 35 U.S.C. §102(b)

Claims 1 and 3 are rejected under 35 U.S.C. §102(b)as allegedly being anticipated by Rasmussen et al. (1996). The rejection states Rasmussen discloses a polynucleotide sequence encoding a portion of the flaA gene of Campylobacter, wherein the

polynucleotide sequence is an oligonucleotide portion of SEQ ID NO:1. The rejection reasons that Rasmussen polynucleotide shares 100% sequence identity with a portion of SEQ ID NO:1, and encodes a portion of the amino acids of SEQ ID NO:2.

RESPONSE

By this Amendment, Claims 1 and 3 are amended, thus rendering the rejection moot.

Amended claim 1 is directed to a polynucleotide sequence encoding an immunogenic polypeptide that is a portion of the flaA coding region of Campylobacter, said polynucleotide sequence comprising nucleotides 13-1015 of the DNA sequence of SEQ ID NO. 1. Newly amended independent claim 3 is drawn to an "isolated and purified" DNA sequence encoding an immunogenic polypeptide comprising amino acid residues 5-338 of SEQ ID No:2.

Rasmussen discloses a PCR diagnostic based on the VC167 sequence. The flaA gene was amplified by PCR from 31 chicken isolates. Oligonucleotide sequences CA1 and CA2 were used as primers in the PCR, were selected from conserved regions of the flagellin gene sequences flaA and flaB of C.coli VC167. The size of the expected products amplified from flaA and flab were 810 basepairs (bp) and 813 respectively.

Rasmussen fails to teach the specific nucleotides of SEQ ID NO: 1 in Claim 1 and the amino acid residues of SEQ ID NO: 2 in Claim 3. Thus, Rasmussen fails to teach each and every element of newly amended claims 1 and 3; therefore, Claims 1 and 3 must

be patentable over Rasmussen.

New Claims 16-24

Newly added claims 16-24 are patentable over the prior art of record because neither Meinersmann, Schultz, Rasmussen, nor Alm teach the specific truncated polynucleotide sequence, 13-1015 of SEQ ID NO:1 or a DNA sequence encoding the immunogenic peptide of amino acid residues, 5-338, of SEQ ID NO:2. Support for new claims 16-17 can be found on page 8, lines 13-16 and pages 8, line 17 through page 9, line 4. Support for new claims 20-21 can be found in Example 3. Support for new bivalent immunogenic composition claims 22-24 can be found on page 15, lines 16-21.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of the claims and to allow all of the claims pending in this application.

If the Examiner has any questions or wishes to discuss this matter, the Examiner is welcomed to telephone the undersigned attorney.

Respectfully submitted,

Date: January 21, 2003

Joseph K. Hemby, Jr.
Reg. No. 42,652
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ATTACHMENT A - MARKED-UP COPY OF SPECIFICATION

Please amend the specification at page 19, line 21 as follows:

Flagella are a key virulence determinant of Campylobacter spp. since motility is essential for establishment of colonization in the mucus[ ]lining of the gastrointestinal tract (25,26,27)

Please amend the specification at page 8, lines 13-21 through page 9, line 4:

Region I of the flaA gene represents the highly conserved N terminal region, and regions II and III represent two regions which are more variable among different sequenced flagellin genes. Regions II and III are not, however, as variable as region IV. The construct was made by amplifying the regions I, II and III using the primer flaA-11 (5'ACCAATATTAACACAAATGTTGCAGCA3') (Seq. ID no. 3) and flaA-2 (5'TTATCTAGACTAATCTCTACCATCATTTTTAAC3') (Seq. ID no.4). The PCR product is digested with the appropriate restriction enzymes in order to insert the product into an expression vector. Any plasmid expression vector, e.g. [pET]PET™(Novogen, Madison Wisconsin) or [pMal]PMAL™ (New England Biolabs, Beverly, MA) and viral expression vectors (e.g. adenovirus, M13, herpesvirus, vaccinia, baculovirus, etc) expression systems can be used as long as the polypeptide is able to be expressed. The PET™ vector is used for the cloning and

over-expression of recombinant proteins in E.coli. In the PET™ system, the cloned gene is expressed under the control of a phage T7 promotor. In the PMAL™ protein fusion and purification system, the cloned gene is inserted into a PMAL™vector downstream from the MALE™ gene, which encodes maltose-binding protein (MBP). This results in the expression of an MBP-fusion protein. The technique uses the strong P_{tac} promotor and the translation initiation signals of MBP to express large amounts of the fusion protein. The PMAL-C2™ series of vectors have an exact deletion of the MALE™ signal sequence, resulting in cytoplasmic expression of the fusion protein. The PMAL-P2™ series of vectors contain the normal MALETM signal sequence, which directs the fusion protein through the cytoplasmic membrane, resulting in periplasmic expression. The preferred expression system is the [pMal-c2]PMAL-C2™ vector (New England Biolabs, Beverly, MA). For insertion into this system the PCR product is digested with SspI and XbaI, purified by agarose gel electrophoresis, and cloned in a commercially available plasmid vector, [pMal-p2]PMAL-P2™ or [pMal-c2]PMAL-C2™ (New England Biolabs, Beverly, MA) which had been digested with XmnI and XbaI. This vector allows for fusion of the fifth codon of the flaA gene to an *Escherichia coli* gene encoding maltose binding protein (MBP). The MBP-FlaA fusion is transcriptionally regulated by a P_{tac} promotor and is induced by growth in isopropylthiogalactoside (IPTG). Several transformants of *E. coli* DH5-alpha, containing plasmids with the appropriate size insert, were sequenced with the [MalE]MALE™

primer(New England Biolabs). The MALE™ primer is used for sequencing downstream from the malE gene across the polylinker. One plasmid with the expected fusion-protein in the correct reading frame to MalE, termed pEB11-2, was purified.

Please amend the specification at page 9, line 11:

Expression of recombinant flaA gene in [pMal-p2/c2]PMAL-P2/C2™ plasmid.